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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-409**

**Statistical Review(s)**

STATISTICAL REVIEW AND EVALUATION  
CLINICAL STUDIES  
(STABILITY)

Date	
NDA #	21-409
Applicant	Merck
Name of Drug	Singulair
Indication	
Document Reviewed	<ul style="list-style-type: none"><li><input type="checkbox"/> Sponsor's cover letter dated 5/21/02: Response to FDA request for information <u>\\CDSESUB1\N21409\N 000\2002-05-21</u></li><li><input type="checkbox"/> Data sets submitted to EDR: <u>\\CDSESUB1\N21409\N 000\2002-05-21\cmcd\datasets</u></li></ul>
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Key Words	Stability

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## Reviewer's Stability Analysis of Singulair

Table 1 describes the batches' characteristics and the upper and lower specifications considered in estimating the expiry-dating period.

**Table 1. Description of Singulair and stability analysis**

Test parameter	Temperature	Humidity	Strength	Package	Lower spec	Upper spec
Assay	25°C, 30°C	60%	4mg			
Moisture	25°C, 30°C	60%	4mg			
	25°C, 30°C	60%	4mg			
Total degradation	25°C, 30°C	60%	4mg			

For more information about sponsor's conclusions and CMC reviewer-proposed specification limits, please see Appendix on page 8.

**Table 2. Estimate of expiry dating period based on assay (4mg, 25°C, 60%RH)**

Fitted Line	Batch	Estimated Expiry Period
$Y = 101.0454 + 0.0157 \times \text{Time}$	1005-42	—
$Y = 100.2666 + 0.0157 \times \text{Time}$	1005-46	—
$Y = 99.9635 + 0.0157 \times \text{Time}$	MR-4218	—
	~MIN~	—

**Figure 1. Estimate of expiry dating period based on assay (4mg, 25°C, 60%RH)**

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**Table 3. Estimate of expiry dating period based on assay (4mg, 30°C, 60%RH)**

Fitted Line	Batch	Estimated Expiry Period
$Y = 101.1268 + 0.0121 \times \text{Time}$	1005-42	—
$Y = 100.5261 + 0.0121 \times \text{Time}$	1005-46	—
$Y = 100.2894 + 0.0121 \times \text{Time}$	MR-4218	—
	~MIN~	—

**Figure 2. Estimate of expiry dating period based on assay (4mg, 30°C, 60%RH)**

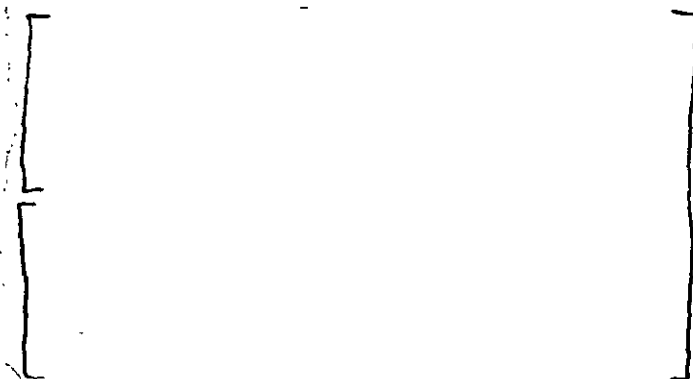
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**Table 4. Estimate of expiry dating period based on moisture (4mg, 25°C, 60%RH)**

Fitted Line	Batch	Estimated Expiry Period
$Y = 0.1931 + 0.0002 \times \text{Time}$	POOLED	—
	—MIN—	—

**Figure 3. Estimate of expiry dating period based on moisture (4mg, 25°C, 60%RH)****Table 5. Estimate of expiry dating period based on moisture (4mg, 30°C, 60%RH)**

Fitted Line	Batch	Estimated Expiry Period
$Y = 0.1817 + 0.0004 \times \text{Time}$	POOLED	—
	—MIN—	—

**Figure 4. Estimate of expiry dating period based on moisture (4mg, 30°C, 60%RH)**

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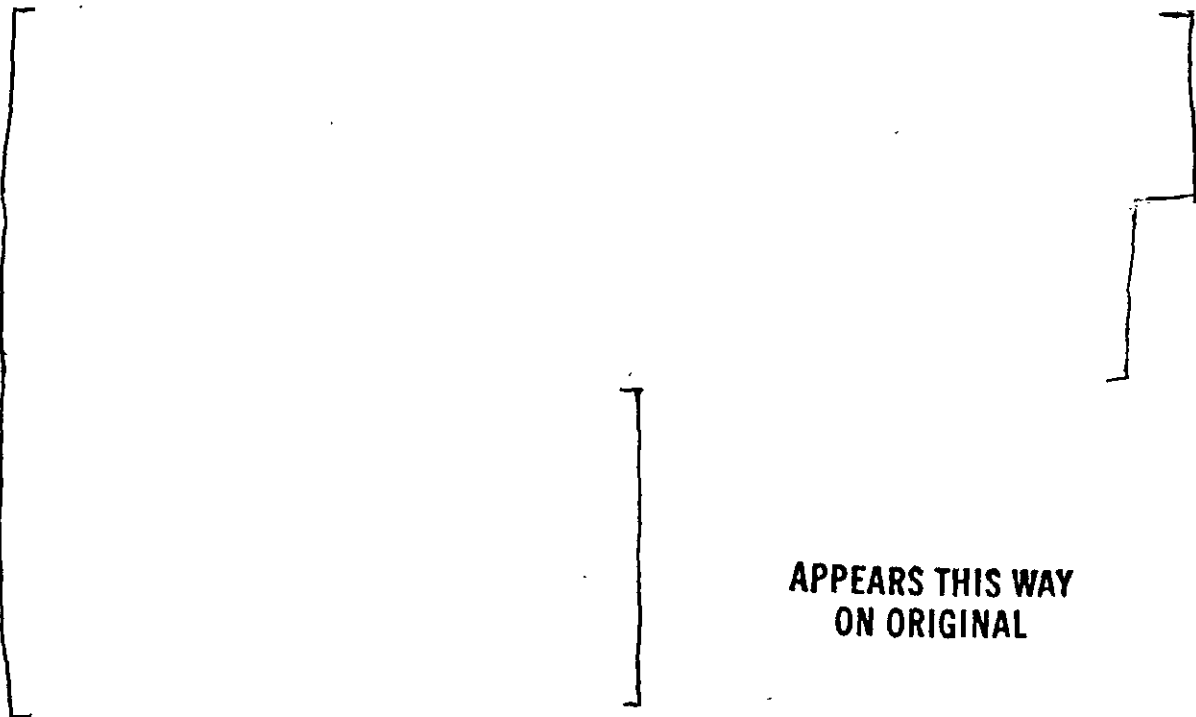
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**Table 6. Estimate of expiry dating period based on — (4mg, 25°C, 60%RH)**

Fitted Line	Batch	Estimated Expiry Period
$Y = 0.3239 + 0.0004 \times \text{Time}$	POOLED	—
	~MIN~	—

**Figure 5. Estimate of expiry dating period based on — (4mg, 25°C, 60%RH)****Table 7. Estimate of expiry dating period based on — (4mg, 30°C, 60%RH)**

Fitted Line	Batch	Estimated Expiry Period
$Y = 0.3591 + 0.0010 \times \text{Time}$	1005-42	—
$Y = 0.2308 + 0.0010 \times \text{Time}$	1005-46	—
$Y = 0.3083 + 0.0010 \times \text{Time}$	MR-4218	—
	~MIN~	—

**Figure 6. Estimate of expiry dating period based on — (4mg, 30°C, 60%RH)**

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**Table 8. Estimate of expiry dating period based on total degradation (4mg, 25°C, 60%RH)**

Fitted Line	Batch	Estimated Expiry Period
$Y = 0.3323 + 0.0002 \times \text{Time}$	POOLED	—
	~MIN~	—

**Figure 7. Estimate of expiry dating period based on total degradation (4mg, 25°C, 60%RH)****Table 9. Estimate of expiry dating period based on total degradation (4mg, 30°C, 60%RH)**

Fitted Line	Batch	Estimated Expiry Period
$Y = 0.3391 + 0.0018 \times \text{Time}$	1005-42	—
$Y = 0.3073 - 0.0007 \times \text{Time}$	1005-46	—
$Y = 0.3079 + 0.0011 \times \text{Time}$	MR-4218	—
	~MIN~	—

**Figure 8. Estimate of expiry dating period based on total degradation (4mg, 30°C, 60%RH)**

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**Table 10. Estimated expiry-dating period**

Test parameter	Condition	Estimated expiry-dating period (in weeks)
Assay	25°C, 60%RH	—
Assay	30°C, 60%RH	—
Moisture	25°C, 60%RH	—
Moisture	30°C, 60%RH	—
—	25°C, 60%RH	—
—	30°C, 60%RH	—
degradation	25°C, 60%RH	—
degradation	30°C, 60%RH	—
	~MIN~	—

## Conclusion

The data show that the estimated expiry-dating period, with 95% confidence, is at least — weeks. The sponsor proposed — expiry dating period was supported by the data.

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Ted Guo  
7/1/02 01:31:44 PM  
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Lisa A. Kammerman  
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BIOMETRICS  
I concur with review

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